Mortality Predicted by different Hematological Malignancy types, Bacteremia, and Lack of Chemotherapy at Kinshasa University Clinics

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Abstract

Objective To identify environmental, pollutant metals, epidemiological, clinical, therapeutic, and able to predict case fatality among patients with anemia and hematological malignancy (HM).

Methods This was a retrospective cohort study in black patient's ≥ 20 years managed for recurrent fever, infections, anemia, and bacteremia between 2009 and 2015 at Kinshasa University Clinics, DRC. The outcomes such as incident HM and case fatality were assessed using univariate means, standard errors, relative risk (RR) and multivariate proportional Hazard ratio (HR) by Cox regression analysis, while Log-Rank test was performed for comparisons by Kaplan Meier curves (means, 95% CI, and median survival).

Results Out of 105 incident HM patients (Male: Female ratio = 1), 57.1% (n= 60) experienced case fatality, There was no association between gender, residence, ethnicity, fever and mortality. There was a significant univariate association between age ≥ 55 years, serum chromium, serum cadmium, serum iodine, serum mercury, rainy season, hemolytic anemia, HM, bone pain, elevated Erythrocyte sedimentation, splenomegaly, abdominal pain, neutropenia, El Nino years, combined local dry season + global climate variability/El Nino, thrombocytopenia, multi-transfusions, bacteremia, lack of chemotherapy, and mortality. After adjusted for confounders using Cox regression models, only incident HM (HR = 16.8; 95% CI, P< 0.0001), Lack of chemotherapy (HR = 6.9, 95% CI, P< 0.002), and Bacteremia (HR= 4.2; 95% CI, P= 0.020) were the most significant and independent predictors of mortality. A separate analysis for HM patients, the mortality rates did not vary (P> 0.05) across HM sub-types: 71.4% (n= 10/14) in multiple myeloma, 84.3% (n= 15/18) in acute myeloid leukemia, 70% (n= 7/10) in myelodysplastic syndromes, 80% (n= 8/10) in chronic myeloid leukemia, 33.3% (n= 2/6) in acute myeloid leukemia, and 80% (n= 4/5) in acute lymphoid leukemia.

Conclusion HM is a major cause of morbidity and mortality with epidemic rates explained by lack of chemotherapy, and recurrent bacteremia among Bantu patients facing aging, climate change, rainy seasons, and lack of palliative care.

Introduction

Cancer is well established as a mass problem in developed countries as well as in developing Sub-Saharan Africa countries (1). Hematological malignancies such as multiple myeloma (MM) leukemia, Hodgkin lymphomas, non-Hodgkin lymphoma (NHL) contribute around 10% of all cancers in Sub-Saharan Africa (2). Moreover, World Health Organization (WHO) report that developing countries are facing the threat of 50% person's death among HM patients (3).

In Sub-Saharan Africa, HM account for 9.9% of cancer deaths (2). Several environment factors (poverty), infections (HIV, Epstein-Barr virus, malaria, and Kaposi sarcoma associated herpes virus, inadequate health systems, lack of early diagnosis, chemotherapy, radiotherapy, stem cell transplantation, supportive care and palliation are associated with burden of mortality and mortality in HM patients from Sub-Saharan Africa (1).

Democratic Republic of Congo (DRC) Central Africa region, is facing emerging incidence of HM due to ageing, exposure to pollution (residence or occupation close to traffic, stations/garages, dust, smoke, or industrial areas) and combined local dry season + global climate variability/ La Nina and combined local dry season + global climate variability/El Nino (4). The most types of those Congolese HM are acute myeloid leukemia (AML), multiple myeloma (MM), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), chronic lymphoid leukemia (CLL), and acute lymphoid leukemia (ALL) (4).

There is also significant association between heavy metal toxicity and HM patients from chaotic urbanization of Kinshasa megacity (5). However, there is no evidence on HM case fatality explained by biological, environment, clinical and pollutant heavy metals in Kinshasa, DRC.

Therefore, the objective of this study sought to identify demographic, environment pollutant heavy metals, and micronutrient deficiency, clinical, therapeutic able to predict specific mortality (case fatality) among confirmed HM patients as well as to investigate prospective values of confirmed HM, unconfirmed HM, local climate and global climate change/variability of incident mortality.

Methods

Study design

This was a retrospective cohort study for 105 confirmed anemic HM from 2010 to 2015 and a prospective cohort for 105 confirmed HM and 50 unconfirmed HM from 2010 to 2015..

Setting

Study population

Patients referred by medical doctors from Kinshasa University Clinics (KUC), Saint Joseph Hospital, Provincial Reference General Hospital of Kinshasa, and private sector Kinshasawide towards Clinic Biological Department.

Sample size

A random sample was calculated as follows: $Ni = 4(Z_{\alpha})^2 P (1- P)/W^2$ with Ni = sample size (Z_{α} = Z- value for two sided α of 0.05 and therefore a confidence interval of 95%, P = proportion of people with chronic anaemia expected to present with incident HM. Thus, the proportion of people with chronic anaemia who present with incident HM in the study population was not known, the authors assumed a proportion of 0.5 which will give the maximum sample size estimate (6), and a width or acceptable error (W) of 0.2. For a two sided α of 0.05 and therefore a confidence interval of 95%, zα = 1.96. So the sample size N = 4(1.96)2(0.5 × 0.5) / 0.04. N = 96 which was approximated to 100.

Allowance for missing data was made: 100 + 20% of potential misses = 120. Inclusion criteria were age ≥ 20 years and myelogram diagnosed HM. Patients with any myelogram result other than HM and those patients who did not wish to participate in the study were excluded.

Laboratory data

HM was defined morphologically using 3.5 mL of blood obtained by venipuncture in tubes with anticoagulant ethylene diamin tetracetic acid (EDTA) for hemogram and myelogram.

Additional three smears of peripheral blood were undertaken. A sample taken from a tube with 3.8% citrate was used for the determination of the erythrocyte sedimentation rate (ESR). The morphological study used ten slides according to the May Grünwald Giemsa (MGG) stains and for the special stains (Sudan black B, Periodic Acid Shift, Coloring of Perls). Medullary smears were also performed for colored staining using the MGG viewed under the multi-ordinary microscope typical of Olympus. iFISH was performed on bone marrow (BM) and peripheral blood (PB) samples patients with chronic myeloid leukaemia (CML), acute myeloid leukaemia (AML) or acute lymphoid leukaemia (ALL) to confirm diagnosis for HM.

Independent predictors were sex, age, heavy metals (Mn, Fe, Ni, Cu, Zn, As, Se, Br, Mo, Cd, I, Hg, Pb), HM types (MM, AML, MDS, CML, CLL, ALL).

Information on gender, age, exposure to traffic pollution and garages or stations, global climate variability (El Nino and La Nina), and local climate (dry and rainy seasons) was obtained. Climate changes caused by global warming conditions caused climate variability, which was defined as short-term fluctuations around the mean climate state. Climate variability also refers to changes in climate patterns such as precipitation, weather conditions, temperature and humidity (7). El Nino Southern Oscillation is associated with climate changes in the tropical and sub-tropical regions as a result of temperature anomalies from the warming and cooling of the ocean surface (8, 9). El Nino can be defined as warmer-than-normal sea or ocean surface temperatures (7) and La Nina refers to cooler-than-normal sea or ocean surface temperatures (7). El Nino years (2009, 2010, 2013 and 2015) and La Nina years (2011, 2012 and 2014) were defined by the THI Oceanic Nino Index (ONI). (http://www.cpc.ncep.noaa.gov/products/analysis_monitoring/ensostuff/ensoyears.shtml). Local climates and seasons were defined by meteorological parameters (monthly temperatures, humidity, winds, fog, and precipitation). The dry season (very dry for June to September and less dry for January to March), cold months and rainy periods (high rainfall for October to December, lower rainfall for April and May) characterized the local climate. The interaction between global climate variability and local climate typically followed the pattern of: local dry season + global La Nina; local dry season + global El Nino; local rainy season + global La Nina; and local rainy season + global El Nino. Places of residence and/or occupation close to high traffic-volume roads, stations/garages, sources of dust, smoke or industrial pollutants were classified as polluted environments. Dependent variable was case fatality.

Statistical analysis

The reliability and validity of this research relies on the accuracy of data and the consistency of the tools and procedures used—the research design. In order to achieve the highest standard of accuracy, the researchers avoided confounding factors and foreseeable information bias and selection bias. In a univariate analysis, continuous variables were symmetrical and expressed as means ± standard deviation (SD), compared between two groups (HM and patients with anaemia but having a normal myelogram) using the Student's t-test. However, categorical variables were presented as frequencies (n = number) and prevalence (%), comparing the two groups using the chi-square test. The researchers performed logistic regression and the Cox regression model to calculate adjusted multivariate hazard ratios (HR = beta exponential) for the risk of incident HM with their corresponding 95% confidence interval (95% CI). Kaplan-Meir curves after the Cox regression model produced a one minus cumulative survival function with a Log-Rank test of the equality of survival distribution and time medians for the different levels of stratified covariates. As age and laboratory optimal cut-off points were unknown, the effective (accurate and sensitive) cut-off values for discriminating HM and normal myelogram were tested a posteriori, using the Receiver Operating Characteristic curves (ROC) method. Diagnostic performance (prognostic) was characterized by the area under the curve (AUC for c-static) was calculated with its corresponding Standard Error (SE), 95% CI, sensibility and specificity. The criterion for two-sided statistical significance was P-value <0.05. All analyses were performed using SPSS software version 23.0 for Windows (IBM/SPSS Inc., New York, USA).

Results

Out of 105 incident HM patients (Male: Female ratio = 1), 57.1% (n= 60) experienced case fatality, There was no significant association (P 0.05) between gender (60.7% males, n = 34/56 vs. 53.1% female, n = 26/49; P = 0.426), residence (rural-semi-urban =51.6% n = 16/31 vs. urban = 52.7% n = 39/74; P < 0.05 = 0.459), copper (P = 0.970), arsenic (P=0.409), manganese (P= 0.590), iron (P = 0.944), nickel (P = 0.459), bromium (P = 0.294), molybdenum (P = 0.998) and specific mortality. There was a significant univariate association (P 0.05) between aging (age ≥ 55 years =78.5% n = 35/44 vs. age< 55 years = 41% n = 25/61; P < 0.0001), ethnicity (DRC West provinces/ Kongo-Ngala = 45.8% n = 27/ 59, DRC Centre provinces/ Luba-Tetela = 71.4%, n= 25/35, DRC East provinces/ Swahili = 72.7% n = 8/22; P= 0.014), environment pollution (remote residence far from erosions-floods-wastes-car = 34.8% n = 8/23, residence closed to traffic gem = 59.6% n = 28/47; closed to erosions-floods-wastes-traffic gem-stations-garages = 68.6% n = 24/35; P = 0.015) and mean level of biomarkers such as serum chromium (P< 0.001), serum cadmium (P<0.0001), serum iodine (P <0001), serum selenium (P<0.0001), serum mercury (P= 0.007), lead (P < 0.0001) elevated erythrocyte sedimentation (P< 0.0001), hemoglobin (P< 0.001), uric acid (P< 0.0001), GGT (P<0.001) (Figure 1), multi-transfusions (P< 0.0001), and hemolytic anemia, HM, bone pain, splenomegaly, abdominal pain, neutropenia, El Nino years, combined local dry season + global climate variability/El Nino, thrombocytopenia, bacteremia, lack of chemotherapy, and mortality (results not shown). However, there was a significant association between combined local climate + global climate

change/variability (rainy season + El Nino = 80% n 8/10; rainy season + La Nina = 78.9%, n = 15/19, dry season + El Nino = 93.3% n = 14/15, dry season + La Nina = 47.4% n = 9/19; P = 0.018) and specific mortality.

Figure 2 shows diagnose performance of optimal cutoffs of biomarkers for micronutrient deficiency/loss of antioxidant capacity (serum zinc, iodine, selenium) and biomarkers for exacerbated oxidative stress/pollutant metal toxicity (serum cadmium, mercury, lead, uric acid, GGT) to discriminate fatal cases and non fatal cases of Hematological Malignancy. Indeed, zinc < 0.30 mg/L (Sensibility = 82%, Specificity = 73%, AUC 0.858; 95% CI 0.788-0.928; P< 0.0001), iodine <0.35 mg/L, (Sensibility = 67%, Specificity = 72%? 0.781 ; 95% CI 0.693-0.869; P< 0.0001), selenium < 0.60mg/L (Sensibility = 93.3%, Specificity 97%, AUC = 0.940 ; 95% CI 0.884-0.996; P < 0.0001), cadmium 2mg/L, (sensibility = 95%, Specificity = 91%, AUC = 0.964 ; 95% CI : 0.927-1.000; P < 0.0001), mercury 1mg/L (Sensibility = 75%, Specificity = 84%, AUC = 0.796 ; 95% CI : 0.709-0.884; P < 0.0001), lead 0.50 mg/L (Sensibility = 80%, Specificity = 82%, AUC = 0.856 ; 95% CI 0.783-0.928; P < 0.0001), uric acid 10mg/dL, (Sensibility = 72%, Specificity = 70%, AUC = 0.689 ; 95% CI 0.581-0.796; P< 0.001), GGT 100 UI/L, (Sensibility = 93.3%, Specificity = 30%, AUC = 0.655 ; 95% CI 0.548-0.762; P = 0.007) were established as optimal cutoffs to predict significantly and precisely specific mortality among HM cases.

After adjusting for confounders using Cox regression models, only incident MH (HR = 16.8; 95% CI, P< 0.0001), Lack of chemotherapy (HR = 6.9, 95% CI, P< 0.002), and Bacteremia (HR= 4.2; 95% CI, P= 0.020) were the most significant and independent predictors of mortality.

In a separate analysis for HM patients, the mortality rates did not vary (P> 0.05) across HM sub-types: 71.4% (n= 10/14) in multiple myeloma, 84.3 % (n= 15/18) in acute myeloid leukemia, 70% (n= 7/10) in myelodysplastic syndromes, 80% (n= 8/10) in chronic myeloid leukemia, 33.3% (n= 2/6) in chronic lymphoid leukemia, and 80% (n= 4/5) in acute lymphoid leukemia.

In considering time for follow-up (dependent variable) of 53.6 ± 3.4 months (Log Rank test P 0.0001) for 105 anemic confirmed HM (exposed) and 50 anemic non confirmed by FISH, incidence mortality as status (vs. survivors), and stratification of covariates by local climate (dry season with months prone to drought vs. rainy season) and global climate change/ variability (El Nino vs. La Nina), Kaplan Meier Kaplan Meier identified dry season with months prone to drought (Figure 3) and El Nino years (Figure 4) as the most significant predictors of lowest survival (dry season = 38.1±45 months 95% CI 29.4-46.9, median = 30 months vs. rainy season = 67.2 ± 4.3 months, 95% CI 58.8-75.5 months; Log Rank P 0.001 and El Nino years = 43.5 ± 6.5, 95% CI 30.8-50 months vs. La Nina = 58.3 ±3.9 months, 95% CI 55.7-65.8; Log Rank P + 0.006).

Discussion

This is the first study in Sub-Saharan Africa to demonstrate burden mortality among Central African patients with HM confirmed by FISH. Demographic factors (aging, ethnic bantu from DRC provinces exposed to wars and ethnic conflicts (Central and East), bacteremia, severe anemia, lack of

chemotherapy, increase in blood transfusion, accelerated ESR, loss of antioxidant capacity-micronutrient deficiency, exaggerated oxidative stress/pollutant metal toxicity, and combined local dry season + El Nino phenomenon. This study highlighted also the importance of FISH to confirm and to invalidate morphologically diagnosed leukemias. As expected, confirmed HM, dry season and El Nino phenomenon were the most significant predictors of survival in this prospective cohort.

HM and covariables as predictors of mortality

The present study identified the environmental, epidemiologic factors (demographic), private clinics, therapeutic and onco-hematologic able to predict mortality due to the HM. With this intention, a retrospective troop was led near the black patients Bantu old of more than 20 years and assumption of responsibility with the CUK for fever, infections, weakens and bacteremia. The incidence of HM and mortality due to the HM were evaluated by using the relative risk (RR) and the risk proportional multivariate (HR) by the regression of Cox, while the test Log-Rank was carried out for the comparisons by the curves of Kaplan-Meier.

The extent of specific mortality (lethality) was also described between various sub-types of HM.

Relative mortality dependent on the HM and other independent predictors

The incidence rate of mortality estimated at 57,1% in the present study between 2009 and 2015, was by far higher and quintuple than the incidence rates (12%) in 2012 (10). Certain studies underline the contribution of the deaths related to the HM estimated at 9,9% of the load of death among all the cases of cancers (HM and other neoplasms) diagnosed in the world (1, 10, 11, 12).

By considering the various forms of HM of this thesis, the incidence rates of mortality related to leukemias were estimated at 78% and the double at those of incidence of the 41,4% in 2011 and those of projections of 42,4% in 2016 in Europe (13). And in the present thesis, fate related to the LLC constituted the scarcity against the surmortality related to the LAM. Some environmental factors, the ethnicity, the life expectancy, the absence of the innovating techniques of diagnosis, competences of the clinicians and the biologists clinicians (medicine of laboratory) and the control of the infectious diseases whose malaria and infection with VIH/SIDA (reduction in antigenic stimulation) explain the disparity of the rates of deaths related to the LLC (14-18).

However, the probability of mortality among the patients reached of LAM estimated at 8/10 in this thesis was similar to that reported in the literature (19).

Climate change leads to over-exposure to ultraviolet rays and lower levels of vitamin D, resulting in decreased levels of immunity. In addition, chronic exposure to benzene products, lead and mercury in the environment increases the risk of HM. Climate change, environmental pollution, aging and anaemic

hypoxia are associated with an imbalance in the anti-oxidant/oxidant state (oxidative stress), which increases the risk of HM incidence (20-30). In addition, Metal ions have been found to interact with cell components such as DNA and nuclear proteins, causing DNA damage and conformational changes that may lead to cell cycle modulation, carcinogenesis or apoptosis (31-33).

Selenium (Se) and zinc (Zn) are essential nutrients that are required for various biochemical and physiological functions such as oxidation-reduction reactions (34).

In some situations, iodine can have an antioxidant power 3 times that of vitamin C, one of the most important exogenous antioxidants. Therefore, any iodine deficiency will lead directly to the decrease or loss of its antioxidant capacity, especially in tissues rich in iodine (placenta, gastric mucosa, breast tissue) (35-37)

Predictors of mortality in the HM

The present study in agreement with the literature, recognized the incidence of HM, the bacteremia (18) and the absence of chemotherapy (17) like the factors of risk (predictors) most significant, independent and significant of the incidence of mortality.

Indeed, the synergy of the effects of the bacteremia and the absence of chemotherapy could explain the univarié risk of mortality doubles and conferred by the HM. But the multivariate risk of mortality conferred by the HM was multiplied by 17 times in the present thesis. Several medullary insufficiencies and/or the overproduction of certain cellular lines are observed in the HM (leucopenia, weakens, thrombopenia, leukocytosis) and often constitute the bed of the complications of an infectious nature (bacterial, mycosis infections), hemorheologic (feeble hypoxia with increase in the number of blood transfusions and disorders of the hemostasis) and cofactors of mortality related to the HM (38, 39).

Moreover, there is a vicious circle between the HM and the bacteremia: the HM being the factor of risk of bacteremia, the bacteremia's are also the factors of risk of mortality related to the HM according to sub-types' of HM per following descending order: LAM (RR ADJUSTED = 23,3; IC 95% 10,0-54,5); MM (RR adjusted = 3,8; IC 95% 1,5-9,3); LLC (RR adjusted = 2,2; IC 95% 0,9-5,1) (18).

The absence of chemotherapy, a recurring reality in DRC and in other countries with limited resources (15-17, 39), explains the excess of mortality in the assumption of responsibility of the HM. The cost of the drugs in the countries with resources limited in general and in DRC in particular constitutes a barrier with their use.

Moreover, there are not data available on the anti-cancer drugs in Africa. An evaluation of the situation in sub-Saharan Africa was tried in 2012, unfortunately it was not crowned success because of many difficulties. On the 22 drugs anti-cancer being on the list of WHO and imported in the Africa area, the majority are credits and are not available all the time. Moreover, these drugs cover only half of the request, which supposes of a shortage of the anti-cancer drugs (17).

Clinical implications and perspective of public health

The present findings from interactions of socio-demographics, environmental factors, pollutant heavy metal toxicity, micronutrient deficiency, oxidative stress, and mortality among patients with HM, will impact DRC health system in term of clinical governance, research, capacity building and prevention of such predictors, incidence, and fatality of HM.

Limitations and strength

This is the first study to identify environmental, pollutant metals, epidemiological, clinical, therapeutic, and able to predict case fatality among patients with anemia and HM.

However, the study was limited to some degree to such extent of unknown predictors not evaluated.

Conclusion

HM is a major cause of morbidity and mortality with epidemic rates explained by lack of chemotherapy, and recurrent bacteremia among Bantu patients facing aging, climate change, rainy seasons, and lack of palliative care.

Declarations

Conflict of interest and financial disclosures

There is no competing financial interests in relation to the work described

Contributors: MSN and BLM were responsible for the conception and design of the study. BLM managed and analyzed the data. JBN, ALK, ANN, PRB, and ACOB collected data. MSN assisted in the acquisition of data and MSN, DKN and BLM provided clinical advice regarding the analysis and interpretation of the data. MSN, PM, JB, and ALK performed samples. YVM, EM, AAA, JS, MSN and BL contributed to the final draft of the paper. All authors read and approved the final manuscript.

Ethics approval: The Ethics Committee of Public Health School of Kinshasa, Faculty of Medicine (ESP/CE/108/15), approved this research. Fully informed and written consent was obtained from all adult participants aged ≥ 20 years. The present study was undertaken in compliance with the Helsinki Declaration (59th WMA General Assembly, Seoul, South Korea, October 2008. http://www.wma.net/en/10 policies/b3/index.html).

References

1. Satish Gopal, William A. Wood, Stephanie J. Lee, Thomas C. Shea, Kikkeri N., Mitsuyasu, Meeting the challenge of hematologic malignancies in sub-Saharan Africa". BLOOD 119, no. 22 (31 May 2012) :5078-

5087, doi: 10.1182/blood-2012-02-387092 2. Ferlay, J; Shin, HR; Bray, F; Mathers, C; Parkin, DM GLOBOCAN 2008, cancer incidence and mortality worldwide: IARC Cancer Base no. 10", Lyon, France International Agency for Research on Cancer 1-2 10 (2008), http://globocan.iarc.fr 3. OMS, CIRC Rapport biennal 2012-2013", (2013), ISBN 978-92-832-0431-2, ISSN 1017-3412 4. Nkanga M.S.N., Longo-Mbenza B., Adeniyi O.V., Ngwidiwo, J.B., Katawandja, A.L.,Kazadi, P.R.B., Nzonzila, A.N., Ageing, exposure to pollution, and interactions between climate change and local seasons as oxidant conditions predicting incident hematologic malignancy at KINSHASA University clinics, Democratic Republic of CONGO (DRC)". BMC 17, no 559 (2017):7, doi : 10.1186/s12885-017-3547-3. 5. Mireille Solange Nganga Nkanga, Benjamin Longo-Mbenza, Jacques Bikaula Ngwidiwo, Antoine Lufimbo Katawandja, Cécile Roth Laure Mapapa Miakassissa, Paul Roger Beia Kazadi and al, Migration toward a chaotic Kinshasa Megacity: effects of Metal toxicity, erosions, floods, wastes, garage stations, working in industries, and the occurrence of cases with hematologic malignancy",Journal of Innovation and Research in Health Sciences & Biotechnology 3 no 1 (September 2017) :473-482, doi: 10.18644/jiresh-biotech.0000046. 6. Chandan, J S, Statistics for Business and Economics", Delhi: Vikas Publishing House, (1998):196–215, https://fr.slideshare.net/khanyasmin/ba-102-applied-operations-research-for-managementdocdocdo 7. Kintoki Mbala F, Longo-Mbenza B, Mbungu Fuele S, et al, Impact of seasons, years el Nino/la Nina and rainfalls on stroke-related morbidity and mortality in Kinshasa", Journal des maladies vasculaires 41, no1 (Février 2016) :4-11, doi: 10.1016/j.jmv.2015.12.002. 8. Zhou, G, Minakana, N, Githeko, AK et al. 2005, Climate variability and malaria epidemics in the highlands of East Africa", Trends in parasitology 21 (2007) : 54-56/ intergovernmental panel on climate change (IPCC), Annual report, doi: 10.1016/j.pt.2004.11.007. 9. Mantilla G, Oliveros H, Barnston AG, The role of ENSO in understanding changes in Colombia's annual malaria burden by region, 1960–2006", Malaria journal 8, no 1 (2009) :6. Doi:10.1186/1475-2875-8-6. 10. Mounia Elidrissi Errahhali, Manal Elidrissi Errahhali, Redouane Boulouiz, Meryem Ourzame and Mohammed Bellaoui, Distribution and features of hematological malignancies in Easten Morocco: A retrospective multicenter study over 5 years", BMC Cancer 16 (2016):159, DOI: 10.1186/s12885-016-2205-5. 11. Facts 2015-2016 The incidence, prevalence and mortality data in Facts 2015-2016" Cancers Facts and Figures Atlanta (2016), GA. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts- figures/cancer-facts-figures-2016. 12. OMS, La fréquence des cancers pourrait augmenter de 50 % dans le monde, avec 15 millions de nouveaux cas en 2020", Centre des médias, (2003), http://www.who.int/mediacentre/releases/2003/pr27/fr/ 13. GP Bodey, M Buckley, YS Sathe, EJ Freireich, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia", Ann Intern Med 64 (1966):328-340, doi: 10.7326/0003-4819-64-2-328. 14. E Gonzalez-Barca, A Fernandez-Sevilla, J Carratala, Salar A, Peris J, Grañena A, Gudiol F. Prognostic factors influencing mortality in cancer patients with neutropenia and bacteriemia", Eur J Clin Microbiol Infect Dis 18 (1999) :539-544, doi https://doi.org/10.1007/s100960050345 15. Russell E. Lewis, Sarah P. Georgiadou1, Fotis Sampsonas, George Chamilos, and Dimitrios P. Kontoyiannis, Risk factors for Early Mortality in Hematological Malignancy Patients with Pulmonary Mucormycosis", Mycoses, 57 no1 (January2014) :17, doi:10.1111/myc.12101. 16. Allen L., De Benoist B, Dary O., Hurrel R. Guidelines on fortification with micronutrients. Edited by WHO Food and Agricultural Organization of the United Nations", Geneva; 2006, http://journals.sagepub.com/doi/abs/10.1177/156482651303400202. 17.

Nestlé Policy on Micronutrient Fortification of Foods & Beverages", Policy Mandatory Public June 2015, https://www.nestle.com/.../nestle-policy-micronutrient-fortification. 18. Sohail Sarwar, Neelam Siddiqui, Waleed Zafar, Sameer Fasih, Abdul Basit, Abdul Hameed, Characteristics and Outcomes of Patients with Chronic Myelogenous Leukemia in Blast Crisis", J Ayub Med Coll Abbottabad 27, no 2 (2015) : 371–4, http://www.jamc.ayubmed.edu.pk. 19. Martin S. Tallman, D. Gary Gilliland, and Jacob M. Rowe. Drug therapy for acute myeloid leukemia", BLOOD 106, no 4 (15 August 2005):1154-1163, doi:10.1182/blood-2005-01-0178. 20. . Fleming AF, Leukemias in Africa", Leukemia, 7 no 2 (1993) :S138–41, https://www.ncbi.nlm.nih.gov/pubmed/8361219. 21. Omoti CE1, Nwannadi AI, Obieche JC, Noma Olu-Eddo A, The Epidemiological features of lymphoid malignancies in Benin City, Nigeria: A 15 years' study", The Pan African Medical Journal 11, no 10 (2012) : doi:10.11604/pamj.2012.11.10.403. 22. Dongre NN, Suryakar AN, Patil AJ, Rathi DB, Occupational lead exposure in automobile workers in North Karnataka (India): effect on liver and kidney functions", Al Ame en J Med Sci 3, no 4 (2010):284–92, http://ajms.alameenmedical.org/articlepdfs/AJMS.3.4.2010.284.pdf. 23. Natelson EA. Benzene-induced acute myeloid leukemia: a clinician's perspective", Am J Hematol 82, no 9 (2007):826–30, doi:10.1002/ajh.20934 https://www.ncbi.nlm.nih.gov/pubmed/17506065. 24. Jomova K, Valko M, Advances in metal-induced oxidative stress and human disease", Toxicology 10, no 283(2-3) (May2011):65–87, doi: 10.1016/j.tox.2011.03.001. 25. Ziello JE, Jovin IS, Huang Y, Hypoxia-Inducible Factor (HIF)-1 Regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia", Yale J Biol Med 80, no 2 (Jun 2007):51–60, PMC2140184, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2140184. 26. Valko M, Morris H, Cronin MT, Metals, toxicity and oxidative stress", Curr Med Chem 12, no 10 (2005):1161–208, https://pdfs.semanticscholar.org/f8d1/ea4e073061c22514353bab2cf596e06904a4.pdf. 27. Reuter S, Gupta SC, Chaturvedi MM, et al. Oxidative stress, inflammation, and cancer: how are they linked?" Free Radic Biol Med 49, no 11 (2010):1603–16, doi: 10.1016/j.freeradbiomed.2010.09.006. 28. Buijsse B, Feskens EJ, Moschandreas J, et al. Oxidative stress, and iron and antioxidant status in elderly men: differences between the South Mediterranean (Crete) and northern Europe (Zutphen.)", Eur. J. Cardiovasc. Prev. Rehab, 14 (2007):495–500, doi: 10.1097/HJR.0b013e3280111e41. 29. Rericha V, Kulich M, Rericha R, David L. Shore, and Dale P. Sandler, incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case–cohort study", Environ Health Perspect 114 (2006):818–22, doi:10.1289/ehp.8476 available via http://dx.doi.org. 30. Muz B, de la Puente P, Azab F, et al, The Role of Hypoxia and Exploitation of the Hypoxic Environment in Hematologic Malignancies", Mol Cancer Res, 12 no 10 (2012) :1347–1354, doi: 10.1158/1541-7786. 31. Chang LW, Magos L, Suzuki T, editors. Toxicology of Metals", Boca Raton. FL, USA: CRC Press; 1996. https://www.crcpress.com/Toxicology-of-Metals-Volume-I/Chang/p/book/9780873718035. 32. Wang S, Shi X, Molecular mechanisms of metal toxicity and carcinogenesis", Mol Cell Biochem, 222 (2001):3–9, doi https://doi.org/10.1007/978-1-4615-0793-2_1. 33. Beyersmann D, Hartwig A., Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms", Arch Toxicol, 82, no 8 (2008):493–512, doi: 10.1007/s00204-008-0313-y. 34. WHO/FAO/IAEA. World Health Organization. Switzerland: Trace Elements in Human Nutrition and Health", Geneva; 1996, http://apps.who.int/iris/bitstream/10665/37931/2/9241561734_eng.pdf. 35. Ling-Zhi Cao; Xiao-Dong Peng, The relationship between iodine intake and the risk of thyroid cancer: A

meta-analysis", Medicine 96, no 20 (May 2017):e6734, doi: 10.1097/MD.0000000000006734. 36. Riesco-Eizaguirre G and Santisteban P., "A perspective view of sodium iodide symporter research and its clinical implications". Eur J Endocrinol 155 (2006):495-512, doi: 10.1530/eje.1.02257. 37. Miller DW. (2006). "Extrathyroidal benefits of iodine", Journal of American Physicians and Surgeons 11, no 4: (2006):106-110 http://www.jpands.org/vol11no4/millerd.pdf. 38. Makani j, Roberts DJ "Hematology in Africa", Hematol Oncol Clin North Am 30, no 2 (2016): 457-75, http://dx.doi.org/10.1016/j.hoc.2015.12.002. 39. A. Jemal, F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman, "Global cancer statistics," CA Cancer Journal for Clinicians 61, no 2 (2011):69–90, doi: 10.3322/caac.21262.

Figures

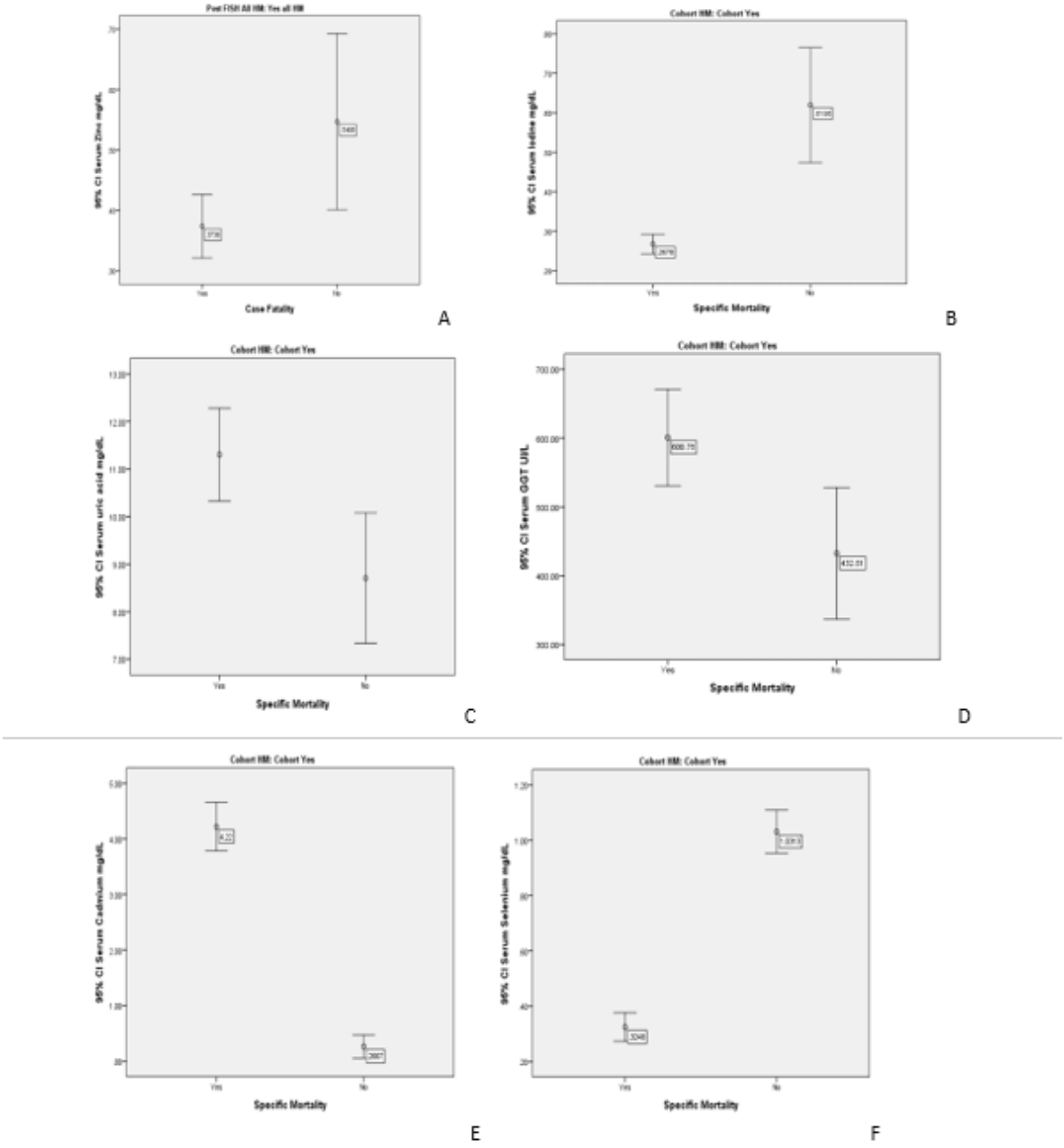

Figure 1. Comparisons of means and 95% CI of zinc, iodine, uric acid, GGT, cadmium and selenium between lethal and non-lethal HM cases.

Figure 1

Comparisons of means and 95% CI of zinc, iodine, uric acid, GGT, cadmium and selenium between lethal and non-lethal HM cases.

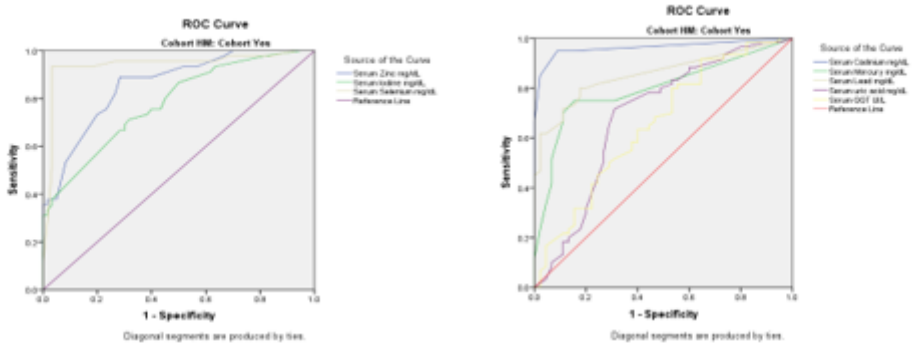

Figure 2. Diagnose performance of optimal cutoffs of biomarkers for micronutrient deficiencies/loss of antioxidant capacity (serum zinc, iodine, selenium) and biomarkers for exacerbated oxidative stress/pollutant metal toxicity (serum cadmium, mercury, lead, uric acid, GGT) to discriminate fatal cases and non fatal cases of Hematological Malignancy.

Figure 2

Diagnose performance of optimal cutoffs of biomarkers for micronutrient deficiencies/loss of antioxidant capacity (serum zinc, iodine, selenium) and biomarkers for exacerbated oxidative stress/pollutant metal toxicity (serum cadmium, mercury, lead, uric acid, GGT) to discriminate fatal cases and non fatal cases of Hematological Malignancy.

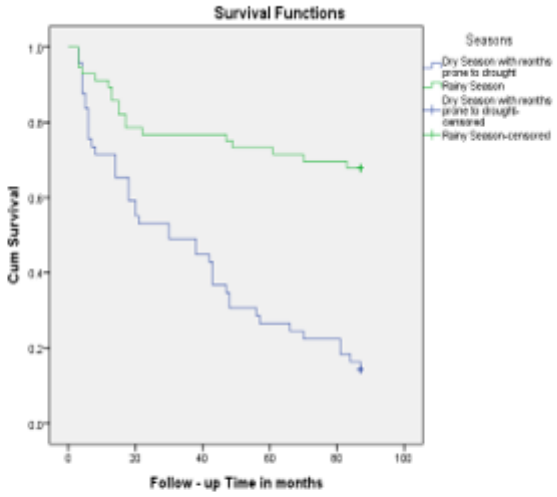

Figure 3. Survival function according to local climate.

Figure 3

Survival function according to local climate.

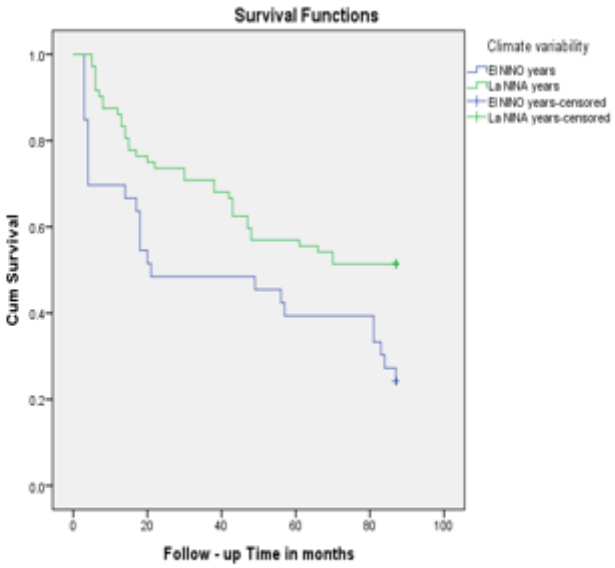

Figure 4. Survival function according to global climate variability.

Figure 4

Survival function according to global climate variability. References